Applicant Is Entitled to Priority Based on His German Patent Applications

The Examiner states that Applicant's claim to foreign priority cannot be granted without certified copies of the foreign priority documents and certified translations. (*See* Office Action, paragraph 6). Certified copies of German Patent Application Nos. 100 18 901.6 and 100 24 830.6 were filed in the Office on April 13, 2001, when the present application was filed. According to 37 C.F.R. § 1.55(4), an English language translation of a non-English language foreign application is not required unless it is necessary to overcome a prior art date relied on by the Examiner during an interference or unless specifically requested by the Examiner. Because the art relied on by the Examiner predates the priority documents, Applicant asserts that a grant of foreign priority is proper without translations of the German documents.

The Claims are Definite

The Examiner rejects claims 10-25 as allegedly indefinite under 35 U.S.C. § 112, second paragraph. (*See* Office Action, paragraph 8). In particular the Examiner asserts that the phrase "mutually overlaps" in claims 10, 13-16, and 20 is indefinite. (*See id.* at paragraph 9). Furthermore, the Examiner contends that the term "universal" in claim 21 is indefinite. (*See id.* at paragraph 10). Finally, the Examiner states that the term "completely" in claim 22 is indefinite. (*See id.* at paragraph 11). Claims 11, 12, 17-19, and 23-25 are also rejected as allegedly indefinite since they depend from claims that have been rejected for indefiniteness. (*See id.* at paragraph 8). In view of the remarks set forth below, Applicant respectfully traverses these rejections.

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"Mutually Overlapping"

The Examiner states that the phrase "mutually overlapping" is vague since it is allegedly unclear what criteria are being used to determine whether or not a nucleic acid sequence mutually overlaps with another. (*See* Office Action, paragraph 9). The Examiner states, for example, that it is not clear whether such sequences must have identical polynucleotide sequences or are merely complementary. (*See id.*). Furthermore, the Examiner asserts that it is not clear whether the overlapping DNA molecules are single or double stranded. (*See id.*).

Applicant asserts that the phrase "mutually overlapping" is well known to those of skill in the art and thus is not vague or indefinite. Claim language must be construed in view of the context in which it is used and in view of how it is used and defined in the specification. In claims 10, 13-16, and 20, the phrase "mutually overlapping" is used in connection with the phrase "oligonucleotide sequence fragments". To one of skill in the art, an oligonucleotide is a single (not double) stranded nucleotide sequence. Furthermore, because the present invention is clearly directed to identifying nucleotide fragments that can be used for DNA amplification methods such as PCR, it is clear that that the fragments are single stranded. It would be illogical, for example, to talk about using double stranded fragments as primers in a PCR reaction, since primers can only be single stranded. Thus, there is no question that one of skill in the art would understand that the phrase "mutually overlapping oligonucleotide sequence fragments" refers to single (not double) stranded fragments.

Furthermore, one of skill in the art, reading the phrase "mutually overlapping" in the context of the rest of the claim, as well as the specification, would understand what

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is meant by this term. On page 3, lines 20-24, the specification describes how sequence fragments, preferably comprising from 30 to 50 "bases", are generated by fragmenting conserved regions of the nucleic acid to be amplified. Because the specification refers to these fragments as "bases", and not "base pairs", it is clear that the oligonucleotides are single stranded.

Finally, because the fragments are all derived from the same original sequence, it is apparent that any two "overlapping" fragments would have identical sequences in the "overlapped" region. In other words, both the sense and anti-sense strands are fragmented at various locations throughout a conserved region so that each resulting fragment contains some portion of the conserved region. When aligned, these single stranded oligonucleotide fragments will "overlap" where they share an identical sequence corresponding to some portion of the conserved region. Thus, in this context, when a particular original sequence is fragmented, it would not make sense to refer to overlapping "oligonucleotide fragments" as having a complementary relationship. Rather, in the context of the entire claim, and as the fragmenting process is described in the specification, one of skill in the art would understand that "mutually overlapping" refers to regions with identical sequences, not sequences that are complementary to each other.

"Universal"

The Examiner states that the term "universal" as used in claim 21 is indefinite since it is unclear what types of bases qualify as "universal". (*See* Office Action, paragraph 10). Claim 21, however, is a dependent claim and specifically states that the "universal base" referred to in claim 20 is inosine. Thus, Applicant assumes the

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Examiner meant to direct the indefiniteness rejection regarding "universal" to claim 20, not claim 21.

Again, Applicant points out that the language used in a claim must be read in view of the specification and in view of the context in which it is used. The specification describes replacing any mismatch base positions with a "universal base" such as inosine so that there is "complete hybridization". (Page 5, lines 4-10). Thus, Applicant asserts that the term "universal base" is not indefinite, especially in view of this description in the specification. A person skilled in the art reading this portion of the specification would understand that a "universal base" is any base that, when used in place of a mismatched base, will result in "complete hybridization". In other words, one of skill in the art knows that there are certain nucleotide bases that will non-selectively pair with any other nucleotide base. As noted in the specification on page 5, line 7, one example of such a "universal base" is inosine.

"Completely"

Finally, the Examiner rejects claim 22, alleging that the term "completely" is vague since it is not clear what criteria are being used to determine whether or not a nucleic acid is "completely hybridized" or not. (*See* Office Action, paragraph 11). Applicant asserts, however, that to one of skill in the art, the term "completely hybridize" is sufficiently clear, especially in view of the specification where this term is described in detail. In particular, page 5, lines 4-10, of the specification describe the process of replacing all mismatched bases with a universal base, such as inosine, "thereby making it possible to achieve complete hybridization." In other words, the purpose of replacing a mismatched base with a universal base such as inosine is to introduce a base that will

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non-selectively pair with other nucleotide bases. Thus, in view of this description, "complete" hybridization can not reasonably mean anything other than 100% complimentarily at each base position - either by virtue of standard Watson-Crick base pairs, or by virtue of a non-selective base such as inosine pairing with any nucleotide base. Thus, when viewed in the context in which it is used in the claim, and in view of the description in the specification, the term "completely hybridize" is not indefinite to one of skill in the art.

According to the above remarks, Applicant respectfully requests that the rejections of claims 10-25 under 35 U.S.C. § 112, second paragraph be withdrawn.

The Claims are not Anticipated by Neri

The Examiner also rejects claims 10-18 and 20-25 as being anticipated under 35 U.S.C. § 102(a) by Neri et al. (U.S. Patent No. 6,194,149). (*See* Office Action, paragraph 13). The Examiner asserts that Neri discloses a method of identifying oligonucleotides to be used in target-dependent reactions by generating overlapping fragments of a conserved region and then determining the similarity of these fragments by sequence alignment. (*See id.* at paragraph 14). Accordingly, the Examiner concludes that claims 10 and 11 are anticipated by Neri. (*See id.*).

Applicant respectfully traverses this rejection. In order to anticipate, a prior art reference must contain each and every element of the rejected claim. *See* M.P.E.P. 2131; *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). In contrast to the Examiner's assertions, claims 10-18 and 20-25 are not anticipated by Neri.

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The Examiner has mischaracterized Neri. Significantly, Neri does not disclose any of the three distinct steps recited in independent claim 10. Instead, Neri is directed to methods of detecting nucleic acid sequence polymorphisms by analyzing the interaction between nucleic acid probes and a folded target nucleic acid strand. This method of "structure probing" (as it is referred to in Neri) takes advantage of the fact that mutations in a nucleic acid sequence will often lead to a different folded secondary structure. By measuring hybridization rates of specific probes with the folded nucleic acid structure, a hybridization signature is identified that, in comparison with other signatures, can be used to detect polymorphisms in the folded target nucleic acid sequence. This overall scheme is described in Figure 1 of Neri, along with the description in column 31 (lines 64-67) through column 32 (lines 1-36).

The Examiner refers to column 46 (lines 50-60) and Figures 18 (a-d) of Neri concluding that claims 10 and 11 are anticipated. (*See* Office Action, paragraph 14). Neri at column 46, lines 50-60, however, simply describes the overall structure of the hepatitis C viral (HCV) RNA genome, mentioning that some regions of the genome are highly conserved, while others are variable. Figures 18 (a-d) show several "bridge" probes indicating where they would hybridize with the predicted structure of the target nucleic acid sequence from HCV. The various bridge probes (b, l, j, k, c and d) were designed to test the effects that different intervening sequences and the inclusion of mismatches would have on hybridization. (*See* Neri, col. 62, lines 5-19).

This does not anticipate claim 10 or 11. Nowhere does Neri describe selecting a target nucleic acid sequence to be amplified (step a) followed by fragmenting one or more conserved regions of this target to produce mutually overlapping fragments (step

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b), and then identifying heterologous sequences that are similar to these fragments (step c). Although Neri discusses a "target sequence" as part of the disclosed method, Neri never describes fragmenting this target sequence. In fact, Neri (col. 31, lines 3-8) teaches just the opposite:

> "Rather than destroying secondary structure by high stringency conditions and target fragmentation, the methods of the present invention use conditions in which the formation of intramolecular structures is favored, i.e., unfragmented target strands in conditions of low stringency."

Furthermore, Neri does not describe identifying heterologous sequences that are similar to the mutually overlapping fragmented sequences as in step (c) of claim 10. Contrary to the Examiner's assertion, Figure 18 shows oligonucleotide probes that were synthesized to compare the effects on hybridization of different nucleotides at the bridging positions and mismatches in the regions that bind to the target nucleic acid sequence. These are **not** sequences that have been identified as being similar to mutually overlapping fragments from an original target sequence to be amplified according to claim 10.

In sum, the disclosure of Neri is unrelated to the present invention. Neri describes methods for using specific oligonucleotide probes to assay for polymorphisms in a target sequence. The present application, on the other hand, discloses a method of finding heterologous primers that can be used in nucleic acid amplification methods. Since Neri does not disclose the three distinct steps outlined in claim 10, neither claim 10 or 11 (which is dependent on claim 10) is anticipated by this reference.

The Examiner further asserts that Figure 18(a) of Neri shows a hepatitis-C viral nucleotide sequence that is identical to SEQ ID NO. 1 of the present application, and

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that accordingly, claims 12-17 are anticipated. (*See* Office Action, paragraph 15). SEQ ID NO. 1 is disclosed in the present application to be 5' - GGT ICA IGG TCT AIG AGA CII CCC GGG - 3'. Applicant has studied Figure 18(a) and simply fails to see where this identical sequence is found. Furthermore, even if Neri did disclose SEQ ID NO. 1, claims 12-17 are still not anticipated because they depend from claim 10. As discussed above, claim 10 is not anticipated by Neri. By definition none of the claims that depend from claim 10 are anticipated either.

The Examiner also asserts that because Neri discloses a record reference library of genetic fingerprints containing nucleic acid sequences (col. 12, lines 36-48) claim 18 is anticipated. (*See* Office Action, paragraph 16). Claim 18 also depends from claim 10 and further adds that the identification step (step c) is performed by use of a gene library. Neri (col. 12, lines 36-48), on the other hand, describes a "reference library" that is created from the hybridization signatures produced using the "structure probing" method. In other words, the "reference library" described in Neri contains captured structures comprising probes complexed with the target nucleic acid sequence. Thus, Neri is describing a completely different concept than that of claim 18. Furthermore, since claim 18 depends from claim 10, it is not anticipated for the same reasons that claim 10 is not anticipated.

The Examiner further states that since Neri discloses oligonucleotide probes comprising universal bases such as inosine (col. 10, lines 20-27; col. 26, lines 11-18) that are used for detection methods (col. 50, Ex. 1), claims 20 and 21 are anticipated. (*See* Office Action, paragraph 17). Although Neri discusses probes that can be synthesized with universal bases such as inosine, these probes are used in the

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"structure probing" method of Neri, which, as discussed above, is entirely different from the present invention, which is directed to identifying heterologous sequences useful for nucleic acid amplification. Applicant again emphasizes that the "structure probing" method of Neri does not teach the three steps recited in independent claim 10 of the present application. Accordingly, claims 20 and 21 (which depend from claim 10) are not anticipated.

Finally, the Examiner asserts that claims 22-25 are anticipated by Neri since it discloses probes that are used for hybridization analysis in HCV genotyping (col. 53, Ex. 3) and since primers are used for PCR reactions (col. 54, lines 61-67 and col. 55, lines 1-15). (*See* Office Action, paragraphs 18-19). Example 3 of Neri describes how the "structure probing" method can be used to screen for and detect various subtypes of the HCV genome. The PCR reactions discussed in Example 3 (col. 54, lines 61-67 and col. 55, lines 1-15) were performed for the purpose of labeling the 5' end of the target HCV sequence with fluorescein. Claims 22-25, on the other hand, are directed to using the heterologous sequences identified by the steps recited in claim 10 as primers for amplifying the target nucleic acid sequence. Again, there is no relationship between Example 3 in Neri and the present claims. Furthermore, claims 22-25 all depend from (either directly or indirectly) claim 10. Thus, because Neri does not recite steps (a), (b), and (c) of independent claim 10, that reference can not anticipate claims 22-25.

For the reasons discussed above, Applicant respectfully requests that the rejection of claims 10-18, and 20-25 under 35 U.S.C. § 102(a) be withdrawn.

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The Claims are not Obvious

Finally, the Examiner rejects claims 10-25 under 35 U.S.C. § 103(a) in view of Neri in combination with Tureci et al. (U.S. Patent No. 6,214,983). The Examiner asserts that Neri discloses all the elements in claims 10-18 and 20-25. (*See* Office Action, paragraph 21). The Examiner further asserts that, although Neri does not disclose identifying oliognucleotide sequences in a DNA sequence library (as per claim 19), claim 19 would have been obvious because Tureci discloses searching the GenBank database to identity nucleic acid molecules. (*See id.* at paragraphs 22-25).

Applicant respectfully traverses this rejection. To make a *prima facie* case of obviousness under 35 U.S.C. § 103(a), the Examiner must establish three elements. First, the Examiner must point to a suggestion or motivation, either in the prior art or in the general body of knowledge, to modify or combine the prior art. Second, there must be a reasonable expectation of success in making the suggested modification. Third, the prior art as modified or combined must teach or suggest all limitations of the claimed invention. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); M.P.E.P. 2142. Judged by these standards, Applicant asserts that the Examiner has not met his burden for establishing a *prima facie* case of obviousness.

Most significantly, the Examiner has failed to show that all elements of the present invention are present in the cited references. As discussed above with respect to anticipation, Neri clearly does not disclose any of the steps recited in independent claim 10. Furthermore, Tureci (col. 4, lines 9-27) describes a GenBank search to identify known sequences that belong to the synaptonemal complex, after which an identified sequence was used to further search an expressed sequence tag (EST)

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database. EST's that were identified were then used to design primers to be used in a RACE analysis. The GenBank search described, however, was not performed using a query sequence, but rather GenBank was searched with functional criteria to find all sequences that were expressed specifically in testis and were associated with meiosis. The searching done in Tureci is very different from the searching involved in claim 19, which involves using mutually overlapping fragments (as prepared according to claim 10) as the query fragments to search a DNA sequence database to find heterologous sequences. Thus, contrary to the Examiner's assertion, Tureci does not disclose identifying heterologous sequences in a DNA database in the context of independent claim 10, from which claim 19 depends.

Thus, the Examiner has failed to show that Neri and Tureci disclose **all** of the elements of independent claim 10, let alone dependent claims 11-25. Furthermore, even if all the elements could be found in these references, the Examiner has not pointed to any teaching or suggestion that Neri and Tureci could be combined successfully. Indeed, Neri and Tureci are directed to seemingly unrelated inventions. While Neri describes a method of detecting polymorphisms in target nucleic acid sequences, Tureci describes the identification of novel nucleic acid sequences that code for proteins involved in cell transformation. It is not clear why one skilled in the art would combine any of the teachings in Neri with those of Tureci. And even if they are combined, as noted above, Neri and Tureci still do not disclose all of the elements recited in the claims of the present invention. Accordingly, a proper obviousness rejection under 35 U.S.C. § 103(a) has not been made and Applicant respectfully requests that the rejection of claims 10-25 be withdrawn.

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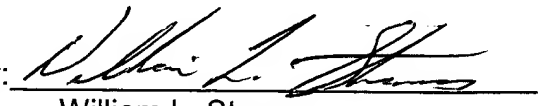
In view of the foregoing remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: July 29, 2003

By: 

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